Remarks

Claims 1-3, 5-8, 12, 13, 15, 18, and 21-29 are currently pending in this applications. All the pending claims have been rejected, in an Office Action mailed March 5, 2008. Claim 21 is amended in the present response.

The Patent Office has rejected claims 1-3, 5-8, 12, 13, 15, 18 and 21-29 under 35 U.S.C. § 112, second paragraph, as being indefinite. Office Action, page 2. According to the Patent Office, the recitation in claim 1 "having a tonicity of from about 100 mosm/kg to about 500 mosm/kg" also requires recitation of an additional tonicity-adjusting agent. The remaining claims were rejected as depending from a rejected claim. Applicants respectfully disagree. A specific tonicity agent is not required in order for the formulation to have the recited tonicity – every solution has a tonicity, and a specific, additional tonicity agent is not needed in order for this to be so. Therefore separate recitation of a specific tonicity agent is not necessary for completeness of the claim. The Patent Office's attention is directed to claim 2, which further limits claim 1 by recitation of "a tonicity-adjusting agent," indicating that claim 1 is not limited to compositions comprising a specific, separate tonicity-adjusting agent. In any event, claim 1 does recite 1,2 propylene glycol, which has the dual function of stabilizing the drug substance in solution and contributing to the tonicity of the solution. See specification, page 5, second full paragraph. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 21 and 22 were also deemed indefinite by the Patent Office due to a lack of antecedent basis in the claims for the claim element "optional tonicity-adjusting agent." Office Action, pages 2-3. Claim 21, from which claim 22 depends, has been amended to recite dependence from claim 2 rather than claim 1, providing the required antecedent basis. This rejection therefore can properly be withdrawn.

The Patent Office has rejected claims 1-3, 5-8, 12, 13, 15, 18 and 21-29 as obvious over the combination of O'Connor et al., US Pat. No. 5,763,394, in view of Asgharian, WO/99/06023. The Patent Office characterizes O'Connor as teaching "a stable pharmaceutically acceptable aqueous formulation containing human grown hormone, a buffer, a non-ionic surfactant, and, optionally, a neutral salt, mannitol, or a preservative." Office Action, page 5. The Patent Office characterizes Asgharian as teaching "topical ophthalmic compositions with provide controlled administration of a drug to the eye ... [which include] ... tonicity agents such as propylene glycol." *Id.* According to the Patent Office, it would have been obvious to a person having ordinary skill in the art to combine the teachings of injectable liquid human growth hormone formulations found in O'Connor with the teachings of the use of propylene glycol in topical ophthalmic gel compositions found in Asgharian, to arrive at the presently claimed invention. Office Action, pages 6-7. The only motivation offered by the Patent Office for combining these teachings is that "O'Connor teaches the elements and the ranges of the hGH formulations and

Asgharian singles out the use of 1,2 propylene glycol for tonicity adjustment." Office Action, page 7. The applicants respectfully traverse this rejection, for the following reasons.

First, the Patent Office has combined teachings from non-analogous art. While O'Connor is a reference within the art of liquid human growth hormone formulations, Asgharian relates to topical gel formulations used specifically for ophthalmic treatments, a very specialized and distinct art. A person working on a liquid growth hormone formulation (which have an intravenous or similar route of administration) would naturally turn to the art relating to liquid formulations of hormones & other peptides which are suitable for injection. Such a worker would *not* turn to the topical ophthalmic art, as such formulations are both physically and functionally completely different from injectable liquid formulations. For example, the formulations of Asgharian, though initially viscous free-flowing liquids, are designed to transition spontaneously to a gel upon administration, thereby providing a controlled release of a therapeutic agent to the eye, along with lubrication and a low level of irritation. Page 4. Such a property could indeed be fatal in an injectable formulation, and at the least would certainly interfere with the proper delivery and distribution of an injected drug. The type and amount of excipients used in such a topical gel formulation differ markedly from the ones used in injectable liquid formulations such as those of the present claims, as the functions they are required to perform – retention of the drug substance on the eye, controlled release of the drug substance to the surface of the eye, stabilization and protection of the drug substance from environmental conditions such as drying, lubrication and protection of the eye from irritation by the drug substance – are completely different than those performed by excipients in injectable liquid formulations (primarily stabilizing of the drug substance during storage, and providing a vehicle for the delivery of the solubilized drug). Thus, a person working on solving the problem of an injectable liquid growth hormone formulation would have absolutely no reason or motivation to turn to the topical ophthalmic gel art for guidance, and indeed would likely avoid that art. This rejection is therefore improper in that it improperly relies on a combination of references from non-analogous art.

Second, even if one were to assume that the topical ophthalmic gel art were sufficiently analogous to be a source of teaching to a person having ordinary skill in the art working to solve the problem of an injectable liquid human growth hormone formulation, there would have been no motivation for such a person to look to the Asgharian reference for its teaching of propylene glycol as a tonicity-adjusting agent. As noted above, the injectable liquid formulations of the present invention are of a fundamentally different nature than the topical ophthalmic gels of Asgharian. The Patent Office has not offered any reasoning as to why a person having ordinary skill in the art would believe that excipients useful in topical ophthalmic gels, for example excipients that function as tonicity agents in such gels, would have a similar function, or any other useful function, in an injectable liquid formulation, and indeed there is no basis for such a belief of which the applicants are aware. In the absence of any reason to turn to a teaching of

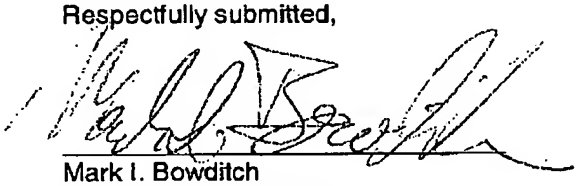
topical ophthalmic gel formulations for guidance in creating an injectable liquid formulation, there can be no motivation to combine the teachings of O'Connor and Asgharian.

Finally, given the very different natures of the injectable liquid growth hormone formulations of the present claims and the topical ophthalmic gel formulations of Asgharian, a person having ordinary skill in the art would not have a reasonable expectations that an excipient which functions as a tonicity agent in a topical ophthalmic gel would work similarly, or indeed function in any useful way, in an injectable liquid formulation. Absent a reasonable expectation that the combination would be successful in solving the problem before her, a person having ordinary skill in the art would not have found it obvious to make the necessary combination of teachings to arrive at the present invention.

Conclusion

For the foregoing reasons, Applicants believe that the claims are in proper form for allowance, and that all of the pending rejections can properly be withdrawn. Favorable action on the claims is earnestly solicited.

Respectfully submitted,



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